REMARKS

Claims 1-8 constitute the pending claims in the present application. Applicants cancel, without prejudice, claims 3, 4, and previously withdrawn claims 9-15. Applicants reserve the right to prosecute claims of similar or differing scope in future patent applications. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action and in the prior Advisory Action.

1. Applicants note with appreciation that the amendments put forth on February 6, 2004 have been entered in full.

2. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Applicants contend that, at the time of filing of the present application, the term "hedgehog polypeptide" was well known and readily understood in the art. In addition to the references cited in the specification and the references cited by the Examiner, Applicants contend that at the time of filing of the instant application well over 1000 papers on the topic had been published. Accordingly, one of skill in the art can readily appreciate the meaning of the term "hedgehog polypeptide" and can readily refer to the literature or to web-based sequence resources such as GenBank to elucidate the nucleic acid or amino acid sequence of a hedgehog polypeptide.

The Office Action directs the Applicants' attention to portions of the specification that allegedly attach a broader meaning to the term "hedgehog polypeptide." The Office Action appears to allege that these portions of the specification make it unclear exactly what is meant by the term "hedgehog polypeptide." Applicants respectfully disagree with the reasoning underlying this rejection. In light of the enormous body of scientific literature relating to hedgehog polypeptides (e.g., sonic, indian, and desert hedgehog) Applicants contend that one or skill in the art would readily appreciate the metes and bounds of the claimed subject matter. Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly

point out that the hedgehog polypeptides for use in the presently claimed methods are hedgehog polypeptides comprising the sequence of a naturally-occurring hedgehog polypeptide, or N-terminal autoproteolytic fragment thereof. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Furthermore, Applicants contend that one of skill in the art would readily appreciate the meaning of the term "dipalmitoyl hedgehog," as recited in the pending claims. The prefix "di" is commonly used throughout the scientific and non-scientific literature to denote two. Accordingly, even an untrained reader would interpret the term "dipalmitoyl hedgehog" to mean a hedgehog polypeptide appended with two palmitoyl moieties. However, the threshold for satisfying the requirements of 35 U.S.C. 112, second paragraph, is not whether an untrained reader would understand the metes and bounds of the claimed subject matter, but whether one of skill in the art would appreciate the metes and bounds of the claimed subject matter.

One of skill in the art is not left to interpret the claims based solely on the plain meaning of the prefix "di," one of skill in the art also has the context provided by the specification and the body of scientific literature. These sources further and unambiguously lead to the obvious interpretation of the term "dipalmitoyl hedgehog" to mean a hedgehog polypeptide appended with two palmitoyl moieties. First, we turn our attention to the evidence provided by the specification. In the Summary of the Invention, Applicants outline that the application discloses the use of hydrophobically-modified hedgehog polypeptides, and as a specific example, dipalmitoyl hedgehog (page 5, lines 26-30). Thus, from the beginning of the application, one of skill would clearly appreciate that the term dipalmitoyl hedgehog refers to a particular hydrophobically modified hedgehog polypeptide. This interpretation is further enforced by the definition of "hydrophobically modified hedgehog polypeptide" and "lipophilic moieties" (page 8, lines 3-6; page 9, lines 20-25). Clearly, a palmitoyl moiety is a lipophilic moiety, as defined by the specification, and as generally appreciated in the art. Clearly, the invention contemplates modifying hedgehog polypeptides with one or more moieties. Thus, in light of the clear guidance provided by the specification, one of skill in the art would readily appreciate that the term "dipalmitoyl hedgehog" refers to one example of a hydrophobically modified hedgehog polypeptide. In this case, the example unambiguously refers to a hedgehog polypeptide modified with two palmitoyl moieties.

Second, Applicants note that the terminology employed in the specification to refer to a polypeptide modified with multiple lipophilic moieties was not unique to the present application, and thus one of skill in the art is also guided by the nomenclature used generally throughout the scientific literature. In fact, prior to the time of filing, researchers throughout the world commonly used terms such as "dipalmitoyl" to refer to the modification of a polypeptide or lipid with two palmitoyl moieties. A quick search of the literature uncovered approximately 100 papers, published prior to the filing date of the instant application, that used the term "dipalmitoyl." By way of example, Applicants enclose herewith the abstracts of a few of these papers (Belsito et al., 2000; Elliott and Prestwich, 2000; Nishijo et al., 2000; Spragg et al., 2000; Ghosh et al., 1990; enclosed with the previously filed response as Exhibits 1-5). Without discussing in detail the content of these publications, the abstracts clearly indicate that reference to modified polypeptides or lipid vesicles using terms such as "dipalmitoyl" was readily and unambiguously employed by many researchers in the art. Accordingly, Applicants' use of similar terminology to refer to the modified hedgehog polypeptides of the present invention readily and unambiguously allows the skilled artisan to appreciate the metes and bounds of the claimed invention.

Applicants do acknowledge that the interchangeable use of the terms "dipalmitoyl hedgehog" and "di-palmitoyl hedgehog" may have introduced unnecessary inconsistency into the claims. Although Applicants contend that the two terms clearly refer to the same modified polypeptide, Applicants have amended the claims to consistently recite "dipalmitoyl hedgehog," as the term "dipalmitoyl" is unhyphenated in many other publications in the art. Applicants' amendment is made purely for consistency and does not narrow the scope of the claims.

Applicants contend that recitation of the terms "naturally-occurring hedgehog polypeptide" and "dipalmitoyl hedgehog polypeptide" are clear and unambiguous. One of skill in the art is guided by both the specification, and by an extensive array of publications in the art at the time of filing of the instant application. Accordingly, the metes and bounds of the claimed subject matter are clear, and Applicants respectfully request reconsideration and withdrawal of this rejection.

3. Claims 1, 2, 4, 6, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Applicants contend that the previously pending claims were enabled throughout their scope. Applicants maintain that the instant specification is broadly enabling, and that one of skill in the art could readily make and test hedgehog polypeptides, fragments, and variants to select suitable compositions for use in the claimed methods. Nevertheless, to expedite prosecution, Applicants have amended the claims to incorporate the features of claim 3 that were previously indicated by the Examiner as constituting enabled subject matter. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. In light of Applicants' amendments to the claims to incorporate the features of claim 3, reconsideration and withdrawal of this rejection are requested.

Applicants note that the claims have been amended to recite that the hedgehog polypeptides are modified with two hydrophobic moieties. Applicants contend that recitation of "two hydrophobic moieties" is supported by the specification, and thus that these amendments do not constitute new matter. Specifically, Applicants direct the Examiner's attention to the definition of "hydrophobically modified hedgehog polypeptide" where the specification clearly contemplates polypeptides modified with **one or more** moieties (page 8, lines 3-6). Given that two moieties fall squarely within the scope of "one or more," Applicants contend that recitation of "two moieties" is implicitly supported by the specification. However, Applicants need not rely on implicit support alone. The working examples provided in the application include **di**palmitoyl sonic hedgehog and **di**palmitoyl Indian hedgehog. Given that the clear meaning of the prefix "di" is two, Applicants contend that working examples of polypeptides modified with two hydrophobic moieties provide explicit support for the amended claims.

5. Claims 1-3 and 8 are rejected under 35 U.S.C. 103(a) as allegedly obvious in light of US Patent No. 5844079 (Ingham et al.). Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Ingham et al. was previously cited by the Examiner as allegedly anticipating the claimed invention. Now, Ingham et al. is being cited by the Examiner as allegedly rendering the claimed

invention obvious. Applicants respectfully disagree with any allegation that the broad teachings of Ingham et al. undermine the patentability of the presently claimed invention.

Applicants contend that a valid patent may issue for a nonobvious species related to a prior patented invention, even though the improvement falls within the disclosure of that prior patent. A prior genus which **does not explicitly** disclose a species does not anticipate a later claim to that species. This position is well supported by the holdings of the Federal Circuit. See, for example, *Corning Glass Works v. Sumitomo Electric U.S.A.*, 868 F.2d 1251, 1262, 9 USPQ2d 1962, 1970 (Fed. Cir. 1989).

Applicants contend that the relationship between the pending claims and the cited art is largely analogous to the factual situation in the above example. Applicants assert that the presently claimed invention provides a particular combination of elements and constitutes a species. Applicants' species is unobvious and patentable over the generic teachings of Ingham et al. because Ingham et al. fail to either teach or suggest the particular combination of elements recited in the pending claims.

Applicants contend that Ingham et al. fail to teach or suggest all the limitations set forth in the claims. Although Ingham et al. is broadly enabling and provides compositions and methods using *hedgehog* polypeptides, Ingham et al. fail to teach the benefits of the particular combinations of specific hydrophobic modifications, formulations, concentration, and method of use set forth in the pending claims. That is, although Ingham et al. broadly teach methods and compositions using *hedgehog* polypeptides, Ingham et al. provide no motivation to specifically select the particular hydrophobic modifications, the particular formulation, the particular concentration, or the particular method of use, as presently claimed. MPEP 2144.08 outlines the guidelines for determining that a reference renders an invention obvious and directs the Examiner to "determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus." Applicants contend that Ingham et al. fail to provide motivation to select the specific class of hydrophobic modifications, the particular formulations, the particular concentration of hedgehog polypeptide, or the particular method of use. Furthermore, Ingham et al. fail to provide motivation to combine each of these particular

elements, as presently claimed. Although the Office Action alleges that one of skill in the art would eventually arrive at the particular concentrations and formulations recited in the pending claims as part of routine optimization, the Examiner has not provided any evidence or additional references that would have motivated one of skill in the art to choose from amongst the embodiments disclosed by Ingham et al. to select these particular elements and arrive at Applicants' invention. The question of whether one of skill in the art would eventual optimize particular parameters to arrive at limitations recited in the claims is irrelevant if one of skill in the art would have never been motivated to select the particular parameters that require optimization.

Applicants maintain that Ingham et al. fail to satisfy the criteria necessary for rendering obvious Applicants' invention. The MPEP and a substantial body of case law clearly recognize the patentability of a species despite the presence of prior art to the genus, as is the case here. Accordingly, the claimed invention is patentable in light of the prior art, and reconsideration and withdrawal of this rejection is respectfully requested.

6. In the Advisory Action mailed September 20, 2004, the Examiner indicated that, if the proposed amendments were entered, claims 1-2 and 8 would be rejected under 35 U.S.C. 103(a) as unpatentable over Ingham et al. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Applicants maintain the arguments of record and contend that Ingham et al. fail to provide motivation to select the particular combination of elements presently claimed from amongst the wide variety of hedgehog polypeptides, modifications, and methods of use disclosed in that reference. Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out certain embodiments of the invention. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Specifically, Applicants have amended the claims to more particularly point out that the modified hedgehog polypeptide is modified with two palmitoyl moieties. Support for the subject matter of this claim is found in previously pending claim 4. Given that Ingham et al. fail to teach or suggest each and every element of the amended claims, Applicants contend that Ingham et al.

fail to anticipate or render obvious the claimed subject matter. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. CIBT-P01-099.**

Respectfully Submitted,

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